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Case Report

Transient Hypoparathyroidism in Diabetic Ketoacidosis

Abstract

Introduction: Diabetic ketoacidosispatients frequently develop a constellation of electrolyte disorders. These patientsare markedly potassium-, magnesium- and phosphate-depleted, but hypocalcemia due to transient hypoparathyroidism was seldom reported previously.

Methods: We describe the clinical history, physical examination findings and laboratory values of the patient and briefly review the relevant literature.

Result: A 43-year-old man with a history of diabetes mellitus presented with vomiting, diarrhea and fatigue for 2 days and his laboratory tests showed high serum glucose and diabetic ketoacidosis. CT scan of the abdomen showed no abnormity. Intravenous fluid resuscitation and continuous insulin infusion was initiated. Omeprazole was started for possible upper gastrointestinal hemorrhage. Hypocalcemia, hypophosphatemia, relative hypomagnesemia and transient hypoparathyroidism occurred in the recovering process of diabetic ketoacidosis. There was neither tetany nor spasmin this patient. Two days after the cessation of omeprazole, his serum total calcium, serum phosphateand PTH all returned to normal range.

Conclusion: Physicians should alert transient hypoparathyroidism in diabetic ketoacidosis patients, especially those treated with proton pump inhibitors.

Abbreviations

DKA: Diabetic Ketoacidosis; PPI: Proton-pump Inhibitor; PTH: Parathyroid Hormone; HHS: Hyperglycemic Nonketotic Hyperosmolar Syndrome

Introduction

Diabetic ketoacidosis (DKA) is characterized by hyperglycemia, metabolic acidosis and increased ketones, caused by starvation of any cause in conjunction with an inter current illness and has been described mainly in type 1 diabetes but also in type 2 and gestational diabetes. Diabetic patients frequently develop a constellation of electrolyte disorders. These patients are often potassium-, magnesium- and phosphate-depleted, especially in the context of diabetic ketoacidosis or hyperglycemic nonketotic hyperosmolar syndrome(HHS). But hypocalcemia due to transient hypoparathyroidism was seldom reported previously. Transient impaired secretion of parathyroid hormone(PTH) from the parathyroid glands can lead to functional hypoparathyroidism, which is commonly seen in profound hypomagnesemia. In this proton-pump era, proton-pump inhibitor (PPI) is commonly used in DKA patients when their first onset is digestive symptom. We report one case of hypocalcemia, hypophosphatemia and transient hypoparathyroidism in diabetic ketoacidosis possibly associated with the use of PPI.

Case Presentation

A 43-year-old man presented to the emergency room with vomiting, diarrhea and fatigue for 2 days. He passed liquid stool more than 30 times a day and only had gruel and soft drinks. His vomit sample contained blood. His medical reviews showed he was diagnosed as diabetes mellitus for 11 years with first onset of thirsty, polydipsia and polyuria. He was prescribed with insulin on diagnosis and in poor treatment compliance. He suffered from diabetic ketosis and acute pancreatitis 2 years ago. Laboratory investigation showed the following: serum glucose 36.2mmol/L, total cholesterol 6.93mmol/L, total triglyceride 2.81mmol/L, low density lipoprotein cholesterol 4.06mmol/L, serumα-amylase 213U/L. On admission, his serum total calcium and magnesium were both within the normal range(Ca^{2+} 2.26mmol/L, reference range 2.00-2.75 mmol/L; Mg^{2+} 1.26 mmol/L, reference range 0.78-1.27 mmol/L), his serum phosphate was a little higher than the upper limit of normalrange (1.84mmol/L, reference range 0.81-1.78 mmol/L). Arterial blood gazes demonstrated metabolic acidosis (pH 6.98, HCO^{3}-<3mmol/L) with negative lactic acid. Further work-up revealed ketonuria (15mmol/L). His $HbA1_C$ was 13.9%. CT scan of the abdomen showed no abnormity. He was diagnosed as diabetic ketoacidosis. Intravenous fluid resuscitation and continuous insulin infusion was initiated. Omeprazole was started for possible upper gastrointestinal hemorrhage. After about six hours of initial fluid resuscitation and continuous insulin infusion, hypocalcemia became obvious and calcium supplement was added into the fluid. One day after intensive fluid resuscitation, pH and bicarbonate level returned to normal range. Urinalysis showed no ketonuria. Serum PTH was severely below the normal range with hypophosphatemia and a decrease of serum magnesium. Standard meal test showed absolute insulin/c-peptide deficiency. He was finally diagnosed as type 1 diabetes mellitus and switched to subcutaneous lispro insulin and glargine insulin treatment. On the four day after admission, fecal occult blood was negative and omeprazole was stopped. We intensively tested the serum electrolyte. On the sixth day after admission, his serum total calcium, serum phosphate and

Table 1: Changes of laboratory test during treatment of diabetic ketoacidosis.

Date and time	Serum total calcium (mmol/L) (2.00-2.75)	Serum phosphate (mmol/L) (0.81-1.78)	Serum magnesium (mmol/L) (0.78-1.27)	PTH (pg/ml) (12-88)	Serum glucose (mmol/L)	CO_2 (mmol/L) (21-35)	pH (7.35-7.45)
1.27(5:23) admission	2.26	1.84	1.26		36.2	undetectable	6.98
1.27(11:34)	1.24	0.27			13.25	6.0	7.20
1.27(17:27)	2.04	0.33			18.26	12.6	
1.27(23:59)	1.86	0.17			9.96	14.3	
1.28(06:00)	2.12	0.13	0.80	3.9	4.98	16.8	7.48
1.30	2.02	0.44			6.66	26.3	
2.1	1.97	0.84			5.97	27.5	
2.2	2.10	0.80		21.4	4.53	29.0	
2.4	2.13	0.90	0.88	20.5	7.31	29.3	
2.3-2.4	24h urine calcium 4.0(mmol/L)	24h urine phosphate 0(mmol/L)					

PTH all returned to normal range. There was neither tetany nor spasmin this patient. Hypocalcemia, hypophosphatemia, relative hypomagnesemia and transient hypoparathyroidism occurred in the recovering process of diabetic ketoacidosis (Table 1). Unfortunately we didn't monitor the serum magnesium level as frequently as we monitored the serum calcium level, so we were unable to figure out the lowest level of serum magnesium. But a U-shape of the serum magnesium level could be predicted based on Table 1.

Discussion

Significant Ca^{2+} and Mg^{2+} losses have been demonstrated during ketoacidosis and the first hours of recovery. Negative Ca^{2+} and Mg^{2+} balance occurs immediately following insulin withdrawal, progresses with acidosis and continues through the first few days of recovery. Martin et al measured serum and urine Ca^{2+} and Mg^{2+} concentrations in 29 patients with ketoacidosis and found that 28% were hypocalcemic when first seen [1]. Balance studies demonstrated that with standard treatment, large amouts of both Ca^{2+} and Mg^{2+} continued to be lost through the urine. After 12h of therapy, 73% of the patients were hypocalcemic and 55% were hypomagnesemic. Since hypocalcemic states are associated with defective pancreatic β-cell insulin release [2], it is possible that the impairment of residual insulin secretion that occurs after ketoacidosis is in part secondary to prolonged negative Ca^{2+} balance. The etiology of Ca^{2+} and Mg^{2+} loss is thought to be osmotic diuresis and the increased mobilization from bone of both ions induced by acidosis [3,4]. Glycosuria, without acidosis, has been shown to triple urinary Ca^{2+} and double urinary Mg^{2+} excretion [5]. Acidosis might also inhibit renal tubular reabsorption of Ca^{2+} ions. Administration of insulin, 0.1U/kg, has been shown to cause small increase in urinary Mg^{2+} excretion [6]. When Mg^{2+} depletion becomes severe, a reversible state of hypoparathyroidism can occur. Hypomagnesemia appears to inhibit both synthesis and releases of PTH and also decreases peripheral responsiveness to PTH [7]. There is evidence that diabetic patientsare relatively hypoparathyroid [8]. In fact, a mild shift downwards in the set-point for PTH secretion in patients with insulin-dependent diabetes mellitus as well as a diminished parathyroid gland responsiveness to hypocalcemia in uremic diabetic patients have been reported [9,10]. The state of hypoparathyroidism would abolish the homeostatic Ca^{2+} control mechanisms that normally maintain serum Ca^{2+} concentrations despite continued loss. The patient in our study had evidence of impaired parathyroid responsiveness.

Decompensated diabetes mellitus with ketoacidosis is associated with excessive phosphate loss due to osmotic diuresis. Despite phosphate depletion, the serum phosphate concentration at presentation is usually normal or even high, because both insulin deficiency and metabolic acidosis cause a shift of phosphate out of cells [11]. Administration of insulin and fluids, and correction of ketoacidosis may reveal phosphate deficiency and cause a sharp decrease in plasma phosphate concentration due to intracellular shift [12]. The routine administration of phosphate during treatment of DKA and HHS is not recommended since randomized trials failed to show any clinical benefit from phosphate administration [12-15]. What is more, correction of hypophosphatemia may have adverse effects, such as hypocalcemia and hypomagnesemia [12,13,16]. Careful phosphate replacement is required in patients with severe hypophosphatemia of less than 1.0 mg/dl (0.32mmol/L) and in patients who develop cardiac dysfunction, hemolytic anemia, or respiratory depression [13,17].

A number of cases of PPI therapy causing hypomagnesemia and hypomagnesemic hypoparathyroidism are reported in literature [18,19]. PPI-induced hypocalcemia maybe due to hypomagnesemia, which may cause a functional hypoparathyroidism, resulting in suppressed parathyroid hormone secretion [20]. It is usually believed that hypomagnesemic hypoparathyroidism does not respond to calcium supplementation until magnesium levels are replenished, but recent case reports show the serum calcium levels normalized before magnesium supplementation was introduced. This sequence of events differed from the typical pattern, which might explain why hypomagnesemic hypoparathyroidism has been unrecognized.

Conclusion

The clinical implication of this case is important. Physicians should alert transient hypoparathyroidism in diabetic ketoacidosis patients. We suggest that magnesium and calcium levels should be measured in diabetic ketoacidosis patients especially those treated with proton-pump inhibitors.

Conflict of Interest

The authors have no multiplicity of interest to disclose.

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